UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,054	11/17/2000	Gerald R. Crabtree	STAN-166	7611

24353 7590 09/21/2005

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 09/716,054	Applicant(s) CRABTREE ET AL.	
	Examiner Lisa V. Cook	Art Unit 1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 8/29/05 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

Request for Reconsideration

1. Applicants response to the Final Office Action mailed April 19, 2005 is acknowledged. Currently claims 16-24 and 40-64 are pending. Claims 40-64 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

2. Currently claims 16-24 are under consideration.

Restriction Requirement

3. Applicant contends that the examiner has constructively elected Group I claims 16-24 for prosecution in the instant invention. However, it is noted that Applicants previously elected claim 16-24 for prosecution on May 22, 2001 and on February 15, 2002.

4. On 2/3/05, Applicant newly submitted claims 40-64 directed to an invention that is independent or distinct from the invention originally claimed. Since applicant had received an action on the merits for the originally presented invention, this invention was constructively elected by original presentation for prosecution on the merits. Accordingly, claim40-64 were withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Applicant traverses the restriction requirement. Applicant does not traverse the Restriction Requirement on the grounds of the claims lacking patentable distinctness. The traversal on the ground(s) "that the entire application can be examined without serious burden to the examiner, is not found convincing.

This is not found persuasive because MPEP § 808.02 recites:

> Where related inventions as claimed are shown to be distinct under the criteria of MPEP § 806.05(c)- § 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof, (B) A separate status in the art when they are classified together, or (C) A different field of search.

In the instant case, (A) -The Restriction Requirement under 35 U.S.C. § 121 in the Final Action mailed 4/19/05 established distinctness of the inventions *(the different methods employ different reagents with distinct binding capabilities which would require separate search and consideration)*:

Specifically, the method of group I utilizes a target protein ligand and blocking protein ligand which specifically bind (T) and (B) respectively (*reading on known and unknown binding specificity*). However the method of group II uses ligands with a specified binding affinity of at least about 10^{-4}M. The invention of group III requires the target protein ligand to specifically bind with an affinity of at least about 10^{-4}M while the blocking protein ligand is a peptidyl-prolyl isomerase. The invention of group IV is further distinct because it employs ligands that are *known to* specifically bind their targets (T) or (B). Accordingly, the methods require different reagents having patentably diverse and distinct binding requirements. Each limitation requires a different search and separate considerations. Therefore the methods are independent and distinct inventions utilizing different reagents and are patentably distinct inventions.

With respect to a different field of search –Please note that the classifications in the restriction are illustrative only and do **not** represent all the classes and subclasses which must be searched for each invention; nor is the search limited to issued US patents, but rather includes published foreign patents and applications as well as literature search.

6. The Restriction Requirement is still deemed proper and is therefore made **FINAL.**

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 16-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically claims 16-24 are drawn to a method of inhibiting a binding event in a host (*in vivo*) via the administration of an effective amount of a non-naturally occurring bifunctional inhibitor molecule.

Although the specification is enabling for the production and *in vitro* utility of non-naturally occurring bifunctional inhibitor molecules (See assay design and results - pages 20-21), it does not reasonably provide enablement for inhibiting protein-protein interactions *in vivo* with said non-naturally occurring bifunctional molecule.

Firstly, the development of non-naturally occurring/synthetic bifunctional molecules with binding characteristics of interest necessitates several conditions which have not been described in the instant specification.

In one instance, the prior art discloses that the development of inhibitors which can bind by both an active site specific interaction to a primary binding site and by a structure nonspecific hydrophobic interaction to a second site (bifunctional or bispecific molecules) requires several parameters to produce the intended binding specificity.

These parameters include; a crystal structure of the enzyme with the bound primary inhibitor, there must be a relatively "open" active site, to permit access to the active site, and the linker must introduce few unfavorable enthalpic and entropic interactions into the bound state. See Jein et al., J Med Chem., 1994, 37, 2100-2105, especially scheme 1 and page 2103, 2nd column 2nd paragraph. These parameters have not been addressed by the instant disclosure. Therefore one of skill in the art would not be able to predict the inhibition by binding of the claimed bifunctional molecule *in vivo*.

Secondly, the specification fails to teach the use of the claimed bifunctional inhibitor molecules in a living organism or host, such that an effective inhibition response is generated. The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host.

In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

Further, the art teaches that successful *in vitro* bifunctional construct binding is not always indicative of the *in vivo* results exhibited by that same bifunctional molecule.

For example, see Peipp and Valerius page 510 – Conclusion, wherein "Results from clinical trials (in vivo effective dosage) with bispecific antibodies are less encouraging". Peipp and Valerius, Biochemistry Society Transactions, 2002, Volume 30, part 4, pages 507-511.

Accordingly, the specification does not provide substantive evidence that the claimed bifunctional molecules are capable of inhibiting a protein-binding event *in vivo*. This demonstration is required for the skilled artisan to be able to use the claimed bifunctional molecules for their intended purpose of preventing protein binding.

Without this demonstration, the skilled artisan would not be able to predict the outcome of the administration of the claimed bifunctional or bispecific non naturally occurring compositions. The ability to reasonably predict the capacity of a single non -naturally occurring bifunctional molecule to prevent protein-protein interaction in vivo is problematic. Unfortunately, the art is replete with instances where even well characterized compositions that induce an in vitro response fails to elicit *in vivo* utility. See Waldmann, Science, Vol.252, 21 June 1991, pages 1657-1662, in particular page 1657 – 2nd column, wherein antibodies binding therapy has proven elusive and only one monoclonal antibody has been licensed for clinical utility. Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful binding composition with out prior demonstration of efficacy.

Thirdly, *in vivo* testing or administration to a host entails considerations for host/patient tolerance, differences, validation, and monitoring; which are not set forth in the disclosure.

The disclosure merely outlines that the non-naturally occurring bifunctional molecule may be used to treat a variety of diseases, including cellular proliferation, autoimmune disease, cardiovascular diseases, hormonal abnormality, infectious disease, and the like without any supporting data/experimentation. See page 19 lines 24-35.

However, Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer antibody biomarker (intermediate end point marker) to have efficacy and success in a clinical application. See page 2716s. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other compositions being administered and tracked in a host/patient.

Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract.

Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease.

"This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section.

Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable.

It has been set forth above that 1) the experimentation required to generate a non-naturally occurring bi-functional molecule which provides binding inhibition such that it would prevent target binding in a living host would be great as 2) there are no immunological experiments provided to demonstrate that the claimed bifunctional compositions are capable of mounting an efficient inhibition response and, more importantly, there are no challenge experiments to demonstrate that a person immunized with any one of the claimed compositions would be treated/protected from a disease.

There are no protocols provided which demonstrate which bifunctional molecules would be effective in immunization, nor are there any protocols detailing the amount of the bifunctional compositions needed to inhibit protein-protein interaction or mount a sufficient immune response in disease treatment, 3) there are no working examples provided in the instant specification, 4) the nature of the invention is a method for producing a non-naturally occurring bifunctional molecule which would provide binding inhibition and treatment in a host, 5) the relevant skill of

those in the art is high yet 6) the state of the prior art has been shown to be highly unpredictable as evidenced by prior art afore mentioned, and lastly 7) the claims broadly encompass the administration of compositions to a host (in vivo) to target protein prevent binding in the host, it is therefore set forth that one of skill in the art could not make and/or use the invention without undue experimentation.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention.

Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

Response to Argument

8. Applicant contends that the reference of Gestwicki et al. cited by Applicants, establishes that inhibition of protein-protein interaction with the bifunctional inhibitor molecule of claims 16-24 can be achieved *in vivo* in a cell. This argument was carefully considered but not found persuasive because Gestwicki et al. does not teach in vivo applications of the bifunctional molecule, but merely set forth in vitro analyses (cultured cells). Applicant is invited to show support for *in vivo* or clinical testing in Gestwicki et al.

Gestwicki et al. do not demonstrate the effects of the bifunctional inhibitor molecule *in vivo* (administration to a host as recited by the instant claims). The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host.

In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

Although Gestwicki et al. establish in vitro cell inhibition with the bifunctional molecules, this does not provide ample guidance with respect to in vivo utility. The prior has shown that *in vitro* response is not sufficient to predict *in vivo* utility. Please see, Peipp and Valerius page 510 – Conclusion, wherein "Results from clinical trials (in vivo effective dosage) with bispecific antibodies are less encouraging". Peipp and Valerius, Biochemistry Society Transactions, 2002, Volume 30, part 4, pages 507-511.

Applicant contends that the method can be practiced without undue experimentation because sufficient description and examples are provided in the report of Gestwicki et al. This argument was carefully considered but not found persuasive because Gestwicki et al. does not teach in vivo applications of the bifunctional molecule, but merely set forth in vitro analyses (cultured cells).

Applicant argues that the quantity of experimentation required to practice the subject invention is reasonable because the art typically engages in such experimentation. This argument was carefully considered but not found persuasive because the specification must teach how to make and use the invention, not teach how to figure out for oneself how to make and use the invention. In re Gardner, 166 USPQ 138 (CCPA 1970). Applicant has not disclosed any methods of using the bifunctional inhibitor *in vivo* to accomplish the claimed outcome.

It is recognized that experimentation is required to optimize methods that have been outlined in protocols for practice, however the instant specification never gives a starting protocol to achieve the desired inhibition. Therefore one of skill in the art would have no clue as to what would be an effective amount of bifunctional molecule to employ, the appropriate route of administration (IP, subcutaneous, IV, oral), or the indicator to measure and determine if the desired effect was achieved (undue experimentation). The prior art teaches that extensive experimentation must be performed to determine efficacy and success in clinical applications (in vivo).

For example see, Ivery (Medicinal Research reviews, 2000, 20(6), 452-484) teaching peptidylprolyl isomerase (PPIases) and immunophilins binding reactions (taught in the instant specification on page 9 lines 9-23 as blocking proteins of particular interest). Ivery discloses that this event has been difficult to elucidate and is still controversial *in vivo*. See abstract.

Also, Tockman (Cancer Research 52:2711s-2718s, 1992) discloses that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. See abstract and page 2716s.

Applicant argues that one skilled in the art would be able to extrapolate the disclosure across the entire scope of the claims without excessive and undue experimentation. This argument was carefully considered but not found persuasive because the invention requires undue experimentation for its practice. The prior art has shown that protein-protein interaction *in vivo* is problematic. The ability to reasonably predict the capacity of a single non -naturally occurring bifunctional molecule to prevent protein-protein interaction in vivo is problematic.

Unfortunately, the art is replete with instances where even well characterized compositions that induce an in vitro response fails to elicit *in vivo* utility. See Waldmann, Science, Vol.252, 21 June 1991, pages 1657-1662, in particular page 1657 – 2nd column, wherein antibodies binding therapy has proven elusive and only one monoclonal antibody has been licensed for clinical utility.

Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful binding composition with out prior demonstration of efficacy.

Applicant contends that protein-protein interaction by administration of a bifunctional inhibitor is well developed and taught by Gestwicki et al. and are therefor unpredictable. This argument was carefully considered but not found persuasive because the specification and Gestwicki et al. do not demonstrate the effects of the bifunctional inhibitor molecule *in vivo*. The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host. In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

Accordingly it is maintained that the practice of the instant invention requires undue experimentation.

9. For reasons aforementioned, no claims are allowed.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lisa V. Cook
Remsen 3C-59
(571) 272-0816
9/12/05

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
09/19/05